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Unclassified  
SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
AD-A209 988			1b. RESTRICTIVE MARKINGS FILE 007		
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE TIC SELECTED			3. DISTRIBUTION/AVAILABILITY OF REPORT distribution list enclosed		
4. PERFORMING ORGANIZATION REPORT NUMBER 1989			5. MONITORING ORGANIZATION REPORT NUMBER(S)		
6a. NAME OF PERFORMING ORGANIZATION Purdue University		6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION Office of Naval Research		
6c. ADDRESS (City, State, and ZIP Code) West Lafayette, Indiana 47907		7b. ADDRESS (City, State, and ZIP Code) Department of the Navy Arlington, VA 22217			
8a. NAME OF FUNDING/SPONSORING ORGANIZATION Office of Naval Research		8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER N00014-89-J-1128		
8c. ADDRESS (City, State, and ZIP Code) 800 North Quincy Street Arlington, Virginia 22217-5000		10. SOURCE OF FUNDING NUMBERS			
		PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
11. TITLE (Include Security Classification) Major Effect of the Leaving Group in Dialkylboron Chlorides and Triflates for the Enolization of Ketones. The Controlled Stereospecific Synthesis of Either [E]- or [Z]-Enol Borinates					
12. PERSONAL AUTHOR(S) Herbert C. Brown, Raj K. Dhar, Raman K. Bakshi, Paul K. Pandiarajan and Bakthan Singaram					
13a. TYPE OF REPORT Technical		13b. TIME COVERED FROM _____ TO _____		14. DATE OF REPORT (Year, Month, Day) March 16, 1989	
				15. PAGE COUNT 8	
16. SUPPLEMENTARY NOTATION					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP	R <sub>2</sub> BCl, R <sub>2</sub> BOtf, synthesis of [E]- and [Z]-enol borinates		
19. ABSTRACT (Continue on reverse if necessary and identify by block number)					
see attached report					
DISTRIBUTION STATEMENT A Approved for public release Distribution Unlimited					
20. DISTRIBUTION/AVAILABILITY OF ABSTRACT <input type="checkbox"/> UNCLASSIFIED/UNLIMITED <input checked="" type="checkbox"/> SAME AS RPT. <input type="checkbox"/> DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION unclassified		
22a. NAME OF RESPONSIBLE INDIVIDUAL Herbert C. Brown			22b. TELEPHONE (Include Area Code) (317) 494-5316		22c. OFFICE SYMBOL

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# Major Effect of the Leaving Group in Dialkylboron Chlorides and Triflates in Controlling the Stereospecific Conversion of Ketones into Either [E]- or [Z]-Enol Borinates

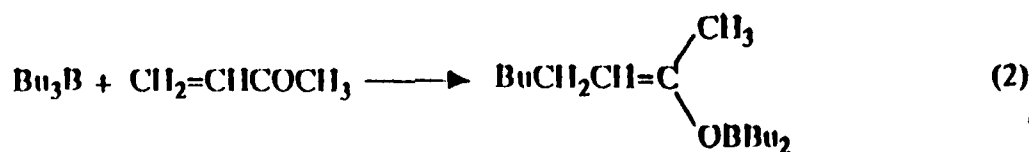
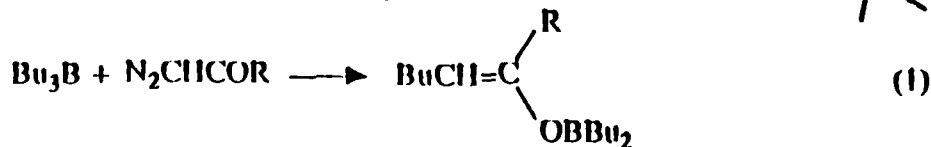
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The ready synthesis and ease of handling of dialkylboron chlorides,  $R_2BCL$ , compared to triflates,  $R_2BOTf$ , give the chlorides a significant advantage as reagents to achieve the conversion of ketones into enol borinates, regiospecifically and quantitatively. This made possible the first study of the effect of changes in the leaving group on the ratios of [E]-:[Z]-enol borinates produced. Indeed, a systematic study of the effect of the steric requirement of the R group ( $R = 9\text{-BBN}$  vs  $Chx_2$ ), the amine ( $Et_3N$  vs  $i\text{-Pr}_2EtN$ ), and the leaving group ( $Cl$  vs  $OTf$ ), with two representative ketones, propiophenone and diethyl ketone, revealed a controlled shift from preferential formation of the [Z]-enol borinates to the [E]-enol borinates. The technique was applied to other representative ketones and selective conversion to both [E]-enol borinates (~80-99%) and [Z]-enol borinates (97-99%) has been achieved.

Enol borinates are valuable intermediates in organic synthesis. A number of published methods have been described for their generation (eqs 1 and 2).<sup>4</sup>

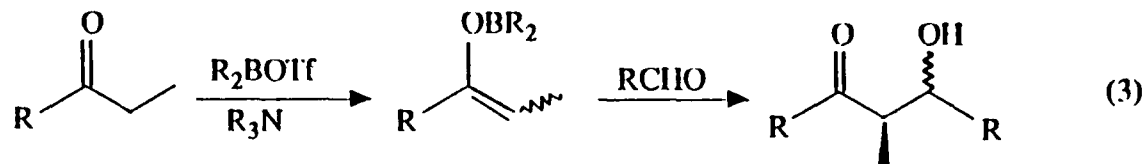


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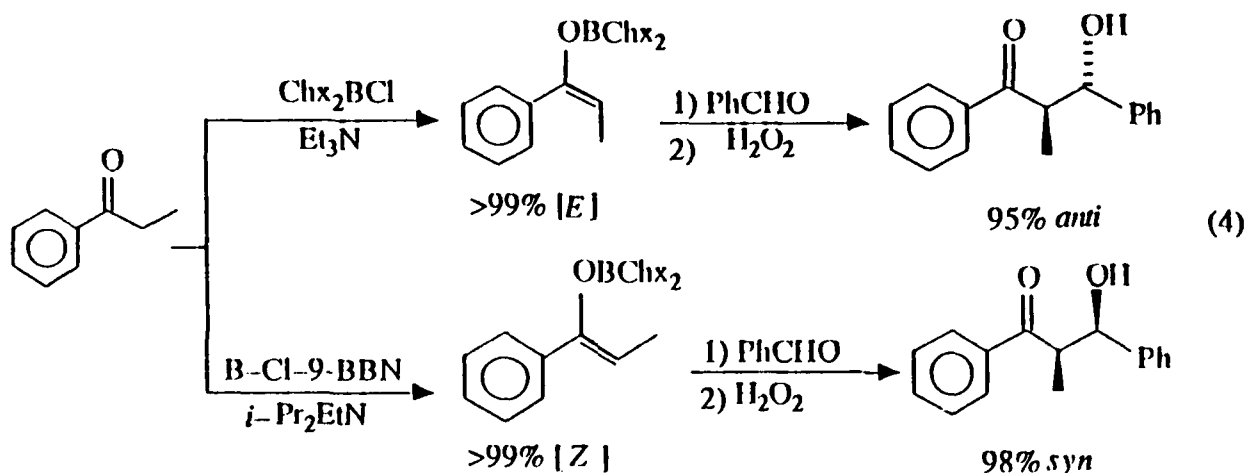
The introduction of dialkylboron triflates,  $R_2BOTf$ , by Mukaiyama greatly facilitated the conversion of ketones directly into the corresponding enol borinates for subsequent conversion into the corresponding aldols (eq 3).<sup>5a</sup>



Fenzl and Köster demonstrated that boron enolate additions are highly stereoselective with the [Z]- and [E]-enolates giving *syn* and *anti* aldols respectively.<sup>6</sup> Later Masamune and Evans used an  $R_2BOTf$  with larger steric requirements, dicyclopentylboron triflate ( $\text{Cpn}_2\text{BOTf}$ ) and achieved an appreciable change in the [Z]- to [E]- ratio of the enol borinate produced from cyclohexyl ethyl ketone.<sup>1,2</sup> Evans subsequently increased the steric requirements of the alkyl group utilizing thexylcyclopentylboron triflate ( $\text{ThxCpnBOTf}$ ), but did not test its effect upon comparable ketones.<sup>2b</sup> Evans and Masamune also examined the effect varying the steric requirements of the amine, but achieved only minor variations in the [Z]- to [E]-enolate product from diethyl ketone. However, Evans and Masamune succeeded in obtaining highly pure [E]-enol borinates (giving *anti* aldol) from thioesters,<sup>1,2</sup> but the synthesis of either pure or predominant [E]-enolates from ketones has remained an unrealized goal.

Thus changes in the steric requirements of both the amine and of the alkyl groups on boron have been examined, but no attention has been given to the effect of the leaving group.

We wish to report that the dialkylboron chlorides in the presence of tertiary amines rapidly and quantitatively convert ketones into the corresponding enol borinates. Moreover, the  $R_2\text{BCl}$  reagents greatly influence the stereochemistry of the enol borinate formed, making it possible to produce preferentially either [Z]- or [E]-enol borinate, leading to the corresponding *syn* or *anti* aldols (eq 4).



Both B-chloro-9-borabicyclo[3.3.1]nonane, B-Cl-9-BBN, and dicyclohexylchloroborane,  $\text{Chx}_2\text{BCl}$ , are readily synthesized.<sup>7</sup> They react readily with ketones in the presence of either  $\text{Et}_3\text{N}$  or  $i\text{-Pr}_2\text{EtN}$ . The reaction is essentially complete in minutes at 0°C, as indicated by rapid formation and precipitation of the amine hydrochloride, along with regiospecific quantitative formation of enol borinate.

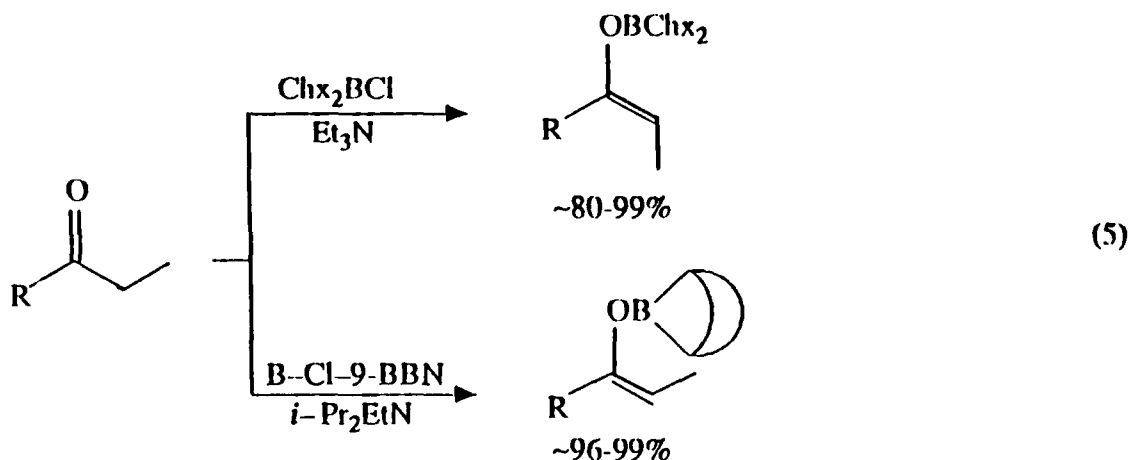
We undertook to make a detailed comparison of the stereochemistry of enolization by triflates and chlorides. The preparation of B-O-Tf-9-BBN was carried out as reported in the literature<sup>5b</sup> and the new reagent,  $\text{Chx}_2\text{BOTf}$ , was prepared as a crystalline solid, mp 88°C.

We adopted diethyl ketone and propiophenone (both previously studied in detail),<sup>1,2</sup> as model ketones, B-X-9-BBN and  $\text{Chx}_2\text{BX}$  (X = OTf and Cl) for the boron reagents, and  $\text{Et}_3\text{N}$  and  $i\text{-Pr}_2\text{EtN}$  for the amines, to examine the effect of these factors on the stereochemistry of enolization. The enolization was carried out at 0°C and the aldol reaction was carried out at -78°C.<sup>8</sup> The data are summarized in Table I. We found it possible to use PMR to determine directly the  $[Z]/[E]$  ratio of enol borinate formed from propiophenone and phenyl benzyl ketone. We were pleasantly surprised to find dicyclohexylboron chloride gave exclusively the  $[E]$ -enol borinate from propiophenone. Moreover, the *syn/anti* ratio of aldols obtained from these two enol borinates corresponds closely to the  $[Z]/[E]$  ratio of the enol borinates formed in the enolization stage as determined by the PMR analysis of the products. In addition, the conversion of a number of cyclic ketones to pure  $[E]$ -enol borinates, required by their cyclic structures, provided aldols

which analyzed predominantly or exclusively for the *anti* aldol products: cyclopentanone, ~100%; cyclohexanone, 98%; cycloheptanone, 97%; cyclooctanone, ~100%. Previous workers in this area have also relied on this method to establish the [Z]/[E] ratio of their enol borinates.<sup>1,2</sup> Consequently, with the additional data now available, it appears safe to conclude that under our conditions, the [Z]/[E] ratio of the enol borinate formed in the enolization can be safely deduced from the *syn* to *anti* ratio of the aldol products for cases where the [Z]/[E] ratio cannot be measured directly.<sup>9</sup>

Our experimental data for the enolization of propiophenone and diethyl ketone by two different R<sub>2</sub>B groups, Chx<sub>2</sub>B- and 9-BBN, two different leaving groups, Cl and OTf, and two different amines, Et<sub>3</sub>N and *i*-Pr<sub>2</sub>EtN, are summarized in Table I. It is seen that the stereochemical outcome of the reaction varies not only with the steric requirements of R<sub>2</sub>B and the steric requirements of the amine,<sup>1,2</sup> but also with the nature of the leaving group, Cl or OTf.

The effect of varying the amine and the alkyl groups on boron are considerably more significant in the case of R<sub>2</sub>BCl than in the case of R<sub>2</sub>BOTf. It is observed that triflates lead to *syn* aldol ([Z]-enol borinate) predominantly, irrespective of the amine used or the steric requirements of the alkyl groups on the boron reagent. On the other hand, Chx<sub>2</sub>BCl and Et<sub>3</sub>N provide the *anti* aldol ([E]-enol borinate) preferentially. Encouraged by these results, the R<sub>2</sub>BCl reagents were applied to several other representative ketones. The results established that the synthesis of either [Z]- or [E]-enol borinate can be achieved with high stereochemical purity (~80-90%) by proper choice of reagent and amine (Table II) (eq 5).



This appears to be the first successful conversion of ketones into enol borinates that are largely or entirely the [*E*]-isomer. This discovery, combined with the fact that the dialkylboron chlorides are readily synthesized and are very stable, makes the methodology here described a valuable procedure for applying the aldol reaction to synthesis. The preferred formation of the [*E*]-enolate over the [*Z*]- is favored by the following: a) use of  $R_2BCl$  instead of  $R_2BOTf$ ; b) use of  $Et_3N$  instead of  $i-Pr_2EtN$ ; c) use of  $Chx_2B$  (larger steric requirements) instead of 9-BBN (smaller steric requirements).

The  $R_2BOTf$  reagents achieve the conversion of representative ketones into pure [*Z*]-enol borinates (leading to the *syn* aldol). However, the  $R_2BCl$  reagents now make possible the conversion of representative ketones into either the essentially pure [*Z*]-enol borinates or the essentially pure or predominant [*E*]-enol borinates, the latter being a transformation not previously available.

**Acknowledgement.** The financial support of the Office of Naval Research is gratefully acknowledged. We thank the Purdue University Biochemical Magnetic Resonance Laboratory for the use of their NT-470-PMR spectrometer (NIH grant RR-01077 and NSF/BBS-8714258).

#### References and Notes

- (1) (a) Von Horn, D. E.; Masamune, S. *Tetrahedron Lett.* **1979**, *24*, 2229. (b) Hirama, M.; Masamune, S. *Ibid*, 2225.

(2) (a) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *Ibid.* **1981**, *103*, 3099.

(3) (a) Reetz, M. T.; Kunish, F.; Heitmann, P. *Tetrahedron Lett.* **1986**, *27*, 4721. (b) Paterson, I.; Lister, M. A.; McClure, C. K. *Ibid.* 4787.

(4) (a) Hooz, J.; Unke, S. *J. Am. Chem. Soc.* **1968**, *90*, 5936. (b) Hooz, J.; Gunn, D. M. *Ibid.* **1969**, *91*, 6195. (c) Kabalka, G. W.; Brown, H. C.; Suzuki, A.; Honma, S.; Arase, A.; Itoh, M. *Ibid.* **1970**, *92*, 712.

(5) (a) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. (b) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174.

(6) Fenzl, W.; Köster, R. *Justus Liebigs Ann. Chem.* **1975**, 1322.

(7) Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1979**, *44*, 2417. (b) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1974**, *73*, 1.

(8) To a 0.5M ether solution of the  $R_2BX$  (5 mmol) and the amine (5 mmol) at 0°C, ketone (5 mmol) was added slowly with stirring. The reaction mixture was then cooled to -78°C, benzaldehyde (5 mmol) was added, and stirring was continued for 2 h. The reaction mixture was warmed to 25°C, the organic phase was separated following addition of water (10 mL) and the solvent was evaporated (25°C, 20 torr). The residue was dissolved in methanol (10 mL) and oxidized with 30%  $H_2O_2$  (3 mL, 25°C, 12 h). It was then extracted with ether, dried over anhydrous magnesium sulfate and the solvent evaporated to give the crude aldol product. The diastereomeric ratio was observed by PMR (470 MHz) analysis of the crude product. The crude aldol product can be further purified by column chromatography over silica gel (~70-80% yield).

(9) It has been reported recently that the stereochemistry of aldol products derived from amide enolates can be influenced by dissolved ammonium salts (ref. 10). In our studies, the ammonium salts separate from the reaction medium essentially quantitatively and have no observable effect on the stereochemistry of the aldol products.

(10) Baker, R.; Castro, J. L.; Swain, C. J. *Tetrahedron Lett.* **1988**, *29*, 2247.

**Table I.** Enolization of Propiophenone and Diethyl Ketone with R<sub>2</sub>BX and Amines<sup>a</sup>

reagent R <sub>2</sub> BX	amine R <sub>3</sub> N	propiophenone		diethyl ketone
		Z:E <sup>c</sup>	syn:anti <sup>d</sup>	syn:anti <sup>d</sup>
B-Cl-9-BBN	Et <sub>3</sub> N	52:48 65:35 <sup>b</sup>	60:40	>99:1
	<i>i</i> -Pr <sub>2</sub> EtN	>99:1	95:5	>99:1
B-OTf-9-BBN	Et <sub>3</sub> N	>99:1	93:7	>99:1
	<i>i</i> -Pr <sub>2</sub> EtN	>99:1	95:5	>99:1
Chx <sub>2</sub> BCl	Et <sub>3</sub> N	<1:99	5:95	21:79
	<i>i</i> -Pr <sub>2</sub> EtN	51:49		72:28
Chx <sub>2</sub> BOTf	Et <sub>3</sub> N	67:33		80:20
	<i>i</i> -Pr <sub>2</sub> EtN	>99:1	98:2	93:7

<sup>a</sup>Enolization at 0°C, except where otherwise noted. <sup>b</sup>Enolization at 25°C. <sup>c</sup>Direct measurement of Z:E ratios of enol borinates by PMR. <sup>d</sup>Measurement of the diastereoselection achieved in the benzaldehyde aldol product.



Table II. Stereoselective Enolization of Representative Ketones with R<sub>2</sub>BCl and Amines

ketone	B-Cl-9-BBN <sup>a</sup>	Chx <sub>2</sub> BCl <sup>b</sup>	yield of [ <i>E</i> ]-isomer, %		ref.
	<i>Z</i> : <i>E</i>	<i>Z</i> : <i>E</i>	present <sup>c</sup>	literature <sup>d</sup>	
propiophenone	>99:1	<1:99	>99	3	2b
phenyl benzyl ketone	>99:1	15:85	85		
isopropyl ethyl ketone	65:35 (98):(2) <sup>e</sup>	<1:99	>99	81	2b
cyclohexyl ethyl ketone	60:40 (96):(4) <sup>e</sup>	<1:99	>99	86	1a
diethyl ketone	>99:1	21:79	79	31	2b

<sup>a</sup>Enolization carried out at 25°C using *i*-Pr<sub>2</sub>EtN. <sup>b</sup>Enolization carried out at 0°C using Et<sub>3</sub>N. <sup>c</sup>Highest conversion to [*E*]-enolate achieved with Chx<sub>2</sub>BCl. <sup>d</sup>Highest conversion to [*E*]-enolate achieved for triflates. <sup>e</sup>*E*/*Z* ratio obtained after equilibration at 25°C of the corresponding enol borinate. For the first two ketones, direct measurement of the *Z*/*E* ratio of enol borinates by PMR; for the other ketones, indirect measurement of *Z*/*E* ratio based upon analysis of the benzaldehyde aldol product.